



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : A61K 38/09, 38/02, 38/10, 38/25, 38/31, C07K 7/23, 2/00, 7/08, 14/60, 14/655	A1	(11) International Publication Number: WO 95/15767 (43) International Publication Date: 15 June 1995 (15.06.95)
(21) International Application Number: PCT/EP94/03904 (22) International Filing Date: 25 November 1994 (25.11.94) (30) Priority Data: P 43 42 092.3 9 December 1993 (09.12.93) DE (71) Applicant (for all designated States except US): ASTA MED-ICA AKTIENGESELLSCHAFT [DE/DE]; An der Pikardie 10, D-01277 Dresden (DE). (72) Inventors; and (75) Inventors/Applicants (for US only): ENGEL, Jürgen [DE/DE]; Erlenweg 3, D-63755 Alzenau (DE). KLOKKERS-BETHKE, Karin [DE/DE]; Tiefenweg 28, D-83661 Lenggries (DE). REISSMAN, Thomas [DE/DE]; Massbornstrasse 44, D-60437 Frankfurt (DE). HILGARD, Peter [DE/DE]; Beethovenstrasse 40, D-60325 Frankfurt (DE).		(81) Designated States: AU, BR, BY, CA, CN, CZ, EE, FI, HU, JP, KR, LT, LV, NO, NZ, PL, RO, RU, SI, SK, UA, US, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE). Published <i>With international search report.</i> <i>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>
(54) Title: LONG-ACTING INJECTION SUSPENSIONS AND A PROCESS FOR THEIR PREPARATION (57) Abstract Poorly soluble salts of LHRH analogues, for example cetrorelix embonate, display an intrinsic sustained release effect in the grain size 5 µm to 200 µm.		

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AT	Austria	GB	United Kingdom	MR	Mauritania
AU	Australia	GE	Georgia	MW	Malawi
BB	Barbados	GN	Guinea	NE	Niger
BE	Belgium	GR	Greece	NL	Netherlands
BF	Burkina Faso	HU	Hungary	NO	Norway
BG	Bulgaria	IE	Ireland	NZ	New Zealand
BJ	Benin	IT	Italy	PL	Poland
BR	Brazil	JP	Japan	PT	Portugal
BY	Belarus	KE	Kenya	RO	Romania
CA	Canada	KG	Kyrgyzstan	RU	Russian Federation
CF	Central African Republic	KP	Democratic People's Republic of Korea	SD	Sudan
CG	Congo	KR	Republic of Korea	SE	Sweden
CH	Switzerland	KZ	Kazakhstan	SI	Slovenia
CI	Côte d'Ivoire	LI	Liechtenstein	SK	Slovakia
CM	Cameroon	LK	Sri Lanka	SN	Senegal
CN	China	LU	Luxembourg	TD	Chad
CS	Czechoslovakia	LV	Latvia	TG	Togo
CZ	Czech Republic	MC	Monaco	TJ	Tajikistan
DE	Germany	MD	Republic of Moldova	TT	Trinidad and Tobago
DK	Denmark	MG	Madagascar	UA	Ukraine
ES	Spain	ML	Mali	US	United States of America
FI	Finland	MN	Mongolia	UZ	Uzbekistan
FR	France			VN	Viet Nam
GA	Gabon				

**Long-acting injection suspensions and a process
for their preparation**

- 5 The invention relates to long-acting injection suspensions containing therapeutically active peptides as physiologically acceptable, X-ray amorphous and crystalline salts of low solubility and to a process for their preparation.

10 In therapy, peptides can often only be used safely and with high bioavailability after parenteral injection since they are destroyed by enzymatic degradation after oral administration; since frequently also with nasal application only a few percent of the dosage applied are absorbed and since, with dermal application, there is no absorption at all.

15 Since peptides only have a very short half life in the organism, the parenteral administration of peptide medicaments, for example LHRH analogs, such as the so-called superagonists and LHRH antagonists, has to be effected daily to achieve the desired effect which consists in the case of both substance groups in the suppression of LH and FSH.

20 The result in men is reduction in testosterone production and, in women, in oestradiol production below a specifically defined set value. The term chemical castration is used.

LHRH analogs are understood to be both superagonists such as goserelin (INN) or triptorelin (INN), as well as antagonists such as cetrorelix (INN), antide (INN) or
25 ganirelix (INN). Goserelin, and the synthesis of goserelin, is described in Drugs of the Future, 5 (4), (1980), p. 191. Buserelin and the synthesis of buserelin is described in Drugs of the Future, 4 (3), (1979), p. 173 and Drugs of Today, 21, (305), (1985). Decapeptyl and the synthesis of decapeptyl is described in Drugs of the Future, 3, (9), (1978), p. 645. Leuprolide and the synthesis of leuprolide is
30 presented in Drugs of the Future 7 (12), (1982), p. 883.

Azaline B is described on pages 13-26 of GHRH-Analogues - The State of the Art (1993), Parthenon Publishing Groups Ed., B. Lunenfeld, V. Insler.

35 There has been no lack of attempts to process long-acting LHRH analogues in formulations having a sustained release effect. GB 2 052 258, for example, describes a formulation which contains the LHRH analogues in sustained release injection forms from the zinc salt of the peptide, sesame oil and aluminium stearate.

The difference between superagonists and antagonists lies in the fact that, in the case of superagonists, a feedback mechanism leads to the effect which is associated in the first weeks of therapy with undesired high hormone release, so-called flare up, which has to be counteracted with additional medication. In contrast, in the case of the antagonists of which cetrorelix (INN) is one, the pharmacological effect occurs immediately and there is no flare up. Lasting reduction in the sex hormone blood level is standard therapy in the palliative treatment of prostate carcinoma and mamma carcinoma to reduce tumour growth in sex hormone-dependent tumours and also a curative treatment in endometriosis. Chemically speaking, the LHRH-superagonists and the antagonists are nona- or decapeptides.

An LHRH antagonist that is effective in the above indication is cetrorelix, a decapeptide of the amino acid sequence Ac-DNal-DpCl-Phe-DPal-Ser-Tyr-DCit-Leu-Arg-Pro-D-Ala-NH₂. Its synthesis and pharmacological properties are described in EP 299 402. Cetrorelix acetate has been identified as the physiologically acceptable salt. It was found in preclinical and clinical studies that the aqueous solution of cetrorelix acetate had to be applied daily in order to lower the hormone level of testosterone or oestradiol to the appropriate extent until the next injection. The duration of action cannot be extended once a threshold dose was reached although a one-week instead of a daily application interval would already be a step forward for chronically sick and non-hospitalised patients.

The state of the art in the use of LHRH-analogues is the daily application of the solution of water-soluble salts as an injection solution or the multiple daily nasal use of buserelin acetate in the form of nose drops (Suprefact nasal) or of nafarelin acetate in nose drop form, which is to date only marketed in the USA. As described hereinabove, it is inherent in these medicinal forms that they have to be used frequently. Injections may only be given by a doctor, the nose drops have to be used several times daily. Both medicinal forms are poorly suited for the treatment of chronic diseases.

DE-OS 42 23 282.1 describes the preparation of a sustained release formulation of cetrorelix embonate by microencapsulation. Implants are medicinal forms permitting longer intervals of use. For example, when implanted under the skin, a cylinder of a biologically degradable poly(lactic acid-glycolic acid) copolymer containing goserelin acetate can effectively lower the testosterone level (Zoladex depot). The monthly injection of a suspension of biologically degradable polymer-particles containing the active substance leuprorelin acetate also effectively lowers the sex hormone blood level over this period (Enantone Monatsdepot^R).

Both sustained release forms are described in the following patents or patent applications. Their obvious disadvantages, apart from the advantage of the intervals between applications, are set out hereinbelow.

5

EP 0 058 481 describes the composition and the preparation of implants marketed under the trademark Zoladex®. The disadvantage of the dosage form lies in the expensive process for manufacturing the cylinders using specially needed extrusion machines and the packaging machines which insert the cylinders into specially
10 designed syringes with extremely thick cannulae. The shape of the cylinder - 1 mm in diameter and several mm long - causes severe pain and haematomas when implanted into the patient. A less painful dosage form is desirable.

EP 0 052 510 describes the composition and preparation of microparticles with, for
15 example, nafarelin acetate. In the presence of chlorinated hydrocarbons the active substance is incorporated into poly(lactic acid, glycolic acid) copolymers. The use of chlorinated hydrocarbons is unavoidable in this composition since the polymers used with the biodegradation performance needed in vivo only dissolves therein. The high residual solvent contents in the medicinal form prepared in this manner of
20 approx. = 1000 ppm are a disadvantage. According to more recent knowledge, chlorinated hydrocarbons are carcinogenic, the residual solvent content in raw materials and medicaments is today limited to <50 ppm according to the current proposal for the European pharmacopoeia (Pharm Europe, Vol. 4, No. 1, March 1992). The process also has the disadvantage that the yield of active substance
25 which is actually incorporated in microcapsules is small due to peptide losses in the aqueous phase which are essential in the process.

Reduction in residual solvent contents below this threshold value, which is desirable in the interest of drug safety, is, if at all, only possible with laborious post-treatment
30 methods. Syntex, for example, has filed a process for residual solvent reduction with subcritical CO₂.

DE 40 23 134 A1 applies a similar peptide incorporation process such as described above in biologically degradable polymers of the type of poly(lactic acid, glycolic
35 acid) copolymers. According to this application, a peptide salt insoluble in water is used instead of incorporating the peptide acetate salt in the polyester to reduce the large active substance losses in this process. Peptide salts cited as being insoluble in water are pamoates, tannates, stearates and palmitates. As already described,

the process has the disadvantage that carcinogenic hydrocarbons have to be used and presents the problem of physiologically unacceptable residual chloromethane or chloroform solvent contents.

- 5 EP 145 240 contains other ways of incorporating water soluble peptide salts. In a complicated process the active substance is incorporated with marked losses in yield from aqueous active substance solution into biologically degradable poly(lactic acids, glycolic acids) copolymers via multiple emulsions, the disadvantage again being the use of chlorinated hydrocarbons.

10

According to EP 505 966, buserelin acetate is embedded in poly(lactic acid, glycolic acid) copolymers via the spray drying of an active substance-polymer solution containing chlorinated hydrocarbons. This process has, in turn, the disadvantage of using carcinogenic chlorohydrocarbons as solvents.

15

When chlorohydrocarbons are used it is not only the high residual solvent amounts in the medicinal form which are a disadvantage, but, from ecological standpoints, the use of these solvents per se, which create disposal problems for the chlorinated hydrocarbons from the manufacturing location and risks for the employees.

20

According to WO 9214449 readily soluble peptides such as growth hormones are incorporated in, for example, lauric acid by mixing active substance with lauric acid, melting down and grinding the mixture to 100 µm particles after cooling. US 5,137,669 produces sustained release forms for LHRH agonists in the same way in order to inject these particles as suspensions for delayed active substance release. A factor common to both formulations is that they need the carrier materials for the longer active substance release and only yield injectable preparations in a laborious process. It has hitherto been impossible to prove the tolerance of the fat deposits, their reliability and the reproducible release of the active substance. In the case of fat embeddings, side effects may occur at the application site in the form of encapsulations which cannot be tolerated in a chronic treatment lasting over several years.

30

- 35 For bromocriptine mesilate, an active substance which is very hard to prepare in sustained release form, DE 3430852 synthesises a new polyester as polyolester of for example glucose with lactic acid and glycolic acid in order to achieve the desired active substance release profile. In this case it was necessary to carry out a comprehensive and costly development and toxicological trials in order to prepare a

sustained release form with sufficient duration of action since it was clear that no simpler and cheaper medicinal form could achieve the same objective.

Embonic acid (4,4'-methylene-bis(3-hydroxy-2-naphtha acid) is frequently used in pharmaceutical formulations in order to formulate poorly dissolving salts of medicaments. These poorly dissolving salts therefore spend longer in the body and give the medicament a sustained release effect. (Römpfs Chemie-Lexikon, Stuttgart 1976, p. 1007).

The formulation of the invention according to claim 1 was surprisingly found to cause an unexpected prolongation of action and improved effect without using biologically degradable polymers or fats. Not only was the duration of action prolonged, measured by the duration of hormone suppression, tumour growth was also found to be suppressed to a supraproportional extent.

The formulation of the invention can also be used in LHRH agonists, for example in leuprolide, buserelin, goserelin and triptorelin. The formulation of the invention may also be used in bombesin antagonists, somatostatin antagonists and GHRH analogs.

The experimental procedure was conducted according to the following procedure:

Inhibitory effect on DMBA (7,12-dimethylbenz[a]-anthracene)-induced mamma carcinoma in Sprague-Dawley rats

Method:

Female Sprague-Dawley rats (animal diet: Altromin R, water ad lib) are given 20 mg 7,12-dimethylbenz[a]-anthracene perorally dissolved in 1 ml olive oil at the age of 50 days using a stomach tube. Tumour appearance is monitored by weekly palpation of the animals. About 90% of the animals develop tumours between the 35th and 70th day after the induction which are suitable for an experimental trial.

Tumour weight was determined using the method by Druckrey, H., Steinhoff, D., Nakayama, M., Preussmann, R., Anger, K. (1983). Experimentelle Beiträge zum Dosis-Problem in der Krebs-Chemotherapie und zur Wirkungsweise von Endoxan, [Experimental contributions to the dose problem in cancer chemotherapy and to the mode of action of Endoxan], Dtsch. Med. Wschr. 88: 651.

The method was validated by comparison between the tumour weights determined by palpation and the tumour weights determined by direct weighing (after tumour excision).

5 The correlation coefficient was 0.98. After the total weights of the tumours had reached about 1 g, the animals were randomised and 7 animals each were allocated to the control and treatment groups.

Treatment began immediately thereafter by subcutaneous injection of the test substances.

10 The hormone status of the animals was determined by means of a vaginal cell smear stained with methylene blue and evaluated according to Jones, T.C., Mohr, U, Hunt, R.D (1972): The genital system, in: Monographs on pathology of laboratory animals sponsored by the International Life Science Institute (Springer, N.Y., London).

15 The experimental results are set out in Figure 1. The curve of the tumour weight for the untreated control animals shows uninhibited increase. Curves 1 (*) and 2 (0) show treatment with cetrorelix acetate in two different carriers. The extended curve 3 shows the drastic reduction in tumour weight after embonate treatment.

20 Since treatment was in this case only in a single dose, the tumour continues to grow because treatment with a single dose is not suitable for killing all tumour cells.

25 The formulation of the invention is an X-ray amorphous precipitate of the decapeptide cetrorelix as an embonic acid salt. The aqueous suspension of this precipitate, which may optionally contain isotonyfying additives, showed a marked prolongation of action in the animal model compared to the aqueous solution of the peptide. It was surprisingly found that the duration of action was about the same as that of an injection suspension that contained the peptide embonate precipitate in a biologically degradable polymer as poly(lactic acid, glycolic acid) copolymers. This
30 result was particularly unexpected since, as set out above, only very laboriously prepared sustained release medicinal forms, which generally contain the active substance in biologically degradable polymers, have hitherto displayed a sufficiently long duration of action.

35 This finding was also surprising since, according to J.Pharm Pharmacol. 47, 878-883 (1985), pyrimethamine, a 2,4-diaminopyrimidine derivative, showed no difference compared to its embonic acid salt in respect of pharmacokinetic behaviour, plasma level course and AUC after subcutaneous injection in mice.

Similarly, imipramine HCl showed no difference to imipramine embonate after oral administration (Indian Journal of Physiology and Pharmacology 25, (4), 331-338 (1989). Crystalline injection suspensions of non-peptide medicinal substances such as prednisolone or triamcinolone are known in sustained release form, as in the case of the crystalline insulin zinc suspension used to treat diabetes. Insulin consists of 51 amino acids. These latter named forms are all crystalline, whereas X-ray diffractometric analysis shows the dosage form of the invention to be amorphous. The particle size of the formulation of the invention lies between 5 μm and 200 μm . A cetorelix embonate with a particle size under 5 μm showed a sustained release effect inferior to that of the formulation of the invention. Similarly, a cetorelix embonate with a particle size of more than 200 μm showed a poorer sustained release effect than the formulation of the invention.

Other advantages of the formulation of the invention consist in higher batch conformity: the quality of the medicament prepared with the formulation of the invention is thus subject to fewer variations.

Example 1

In an equimolar ratio of peptide (calculated as free base) to embonic acid, an aqueous solution of embonic acid containing alkali in excess is combined with the acetate cetorelix acetate solution, embonic acid precipitating as yellow crystals. On addition of dilute sodium hydroxide solution up to pH 7 - 7.5, the embonic acid dissolves and precipitates with the decapeptide as aqueous cetorelix embonate salt of the molar composition peptide : embonic acid 2:1 (Mol/Mol). The precipitate is filtered off, washed with H₂O and dried.

Example 2

Cetorelix acetate and embonic acid are dissolved in equimolar proportions in dimethylacetamide and the solution is dropped into water. The white precipitate of the cetorelix embonate peptide : embonic acid 2:1 (Mol/Mol) is filtered off and dried.

Example 3

Cetorelix and embonic acid are dissolved in a molar ratio of 1:1.6 in a mixture of dimethyl acetamide and optionally water and the solution dropped into water. The yellow precipitate is filtered off and dried. The precipitate obtained is pasted with 70% ethanol, dried at 35°C and sieved through a sieve of mesh size 80 to 125 μ m.

Example 4

The alkaline embonate solution is added to the aqueous ethanolic solution of the peptide acetate in the molar ratio peptide : embonic acid 2:1. The white precipitate is filtered off and dried. The dried precipitate is moistened with 50% ethanol, dried in a vacuum drying cabinet and sieved. The white product contains the 2:1 peptide embonate salt (Mol/Mol).

Example 5

The alkaline embonate solution is added to the aqueous ethanolic solution of the peptide acetate in the molar ratio peptide : embonic acid 1:1.6. The yellow precipitate is filtered off and dried. The dried precipitate is moistened with 50% ethanol, dried in a vacuum drying cabinet at 35°C and sieved. The yellow product

contains the 2:1 peptide embonate salt (Mol/Mol) in addition to the excess of embonic acid.

Experiments on duration of action in the animal:

5

Suspensions of the precipitates were applied subcutaneously to male rats in the dose 0.5 mg cetorelix/kg body weight and determined after application as a measure of the effect of the peptide on testosterone plasma levels. The effect of the cetorelix consists in reduction of the testosterone level. As a reference an injection
10 suspension was tested as well, that prepared according to DE 4023134 A1 and which contained the peptide embonate in poly(lactic acid, glycolic acid) copolymers. The duration of action of a non-sustained release dosage form of cetorelix was determined via examination of the aqueous solution of cetorelix acetate.

15

Figure 3 shows the course of the testosterone level over 300 h determined in male rats after application of the aqueous solution of cetorelix acetate (D-20761). The effect of testosterone suppression is achieved 6 h after the application. Suppression under 1 ng/ml could still be determined in two animals for 24 h, in three further animals up to 48 h or two days.

20

Figure 2 shows the testosterone level over 300 h in four animals (No. 11-14) after applying the same dose of cetorelix as a suspension of cetorelix embonate (D-20762) without viscous additives prepared according to Example 1 (D-20762). The testosterone suppression is also achieved 6 h after the application, the levels rise
25 above 1 ng/ml in one animal after 192 h (eight days), in the other three animals it reliably continues until the ninth day.

25

Figure 4 shows the course of the testosterone level of rats treated with the embonate of the invention (grain size: 80 μ m - 125 μ m).

30

Comparison of Figures 2-3 with Figure 4 immediately shows the advantage of the formulation of the invention.

**Long-acting injection suspensions and a process
for their preparation**

5 Claims

1. A poorly soluble salt of an LHRH analogue, characterized in that the particle size of the particles lies predominantly between 5 and 200 μm .
- 10 2. A poorly soluble salt of an LHRH-analogue, characterised in that the particle diameter of the particles lies predominantly between 10 and 150 μm .
3. A poorly soluble salt of an LHRH-analogue, characterised in that the particle diameter of the particles lies predominantly between 20 and 125 μm .
- 15 4. A poorly soluble salt according to one of Claims 1-3, characterized in that embonic acid is used as salt former.
5. The use of the poorly soluble salt according to one of Claims 1-4 to prepare medicaments.
- 20 6. A salt according to one of Claims 1-5, characterized in that cetrorelix is used as LHRH analogue.
- 25 7. A salt according to one of Claims 1-5, characterized in that antarelix is used as LHRH analogue.
8. A salt according to one of Claims 1-5, characterized in that ganirelix is used as LHRH analogue.
- 30 9. A salt according to one of Claims 1-5, characterized in that antide is used as LHRH analogue.
10. A salt according to one of Claims 1-5, characterized in that A-75998 is used as LHRH analogue
- 35 11. A salt according to Claims 6-10, characterized in that embonic acid is used as salt former.

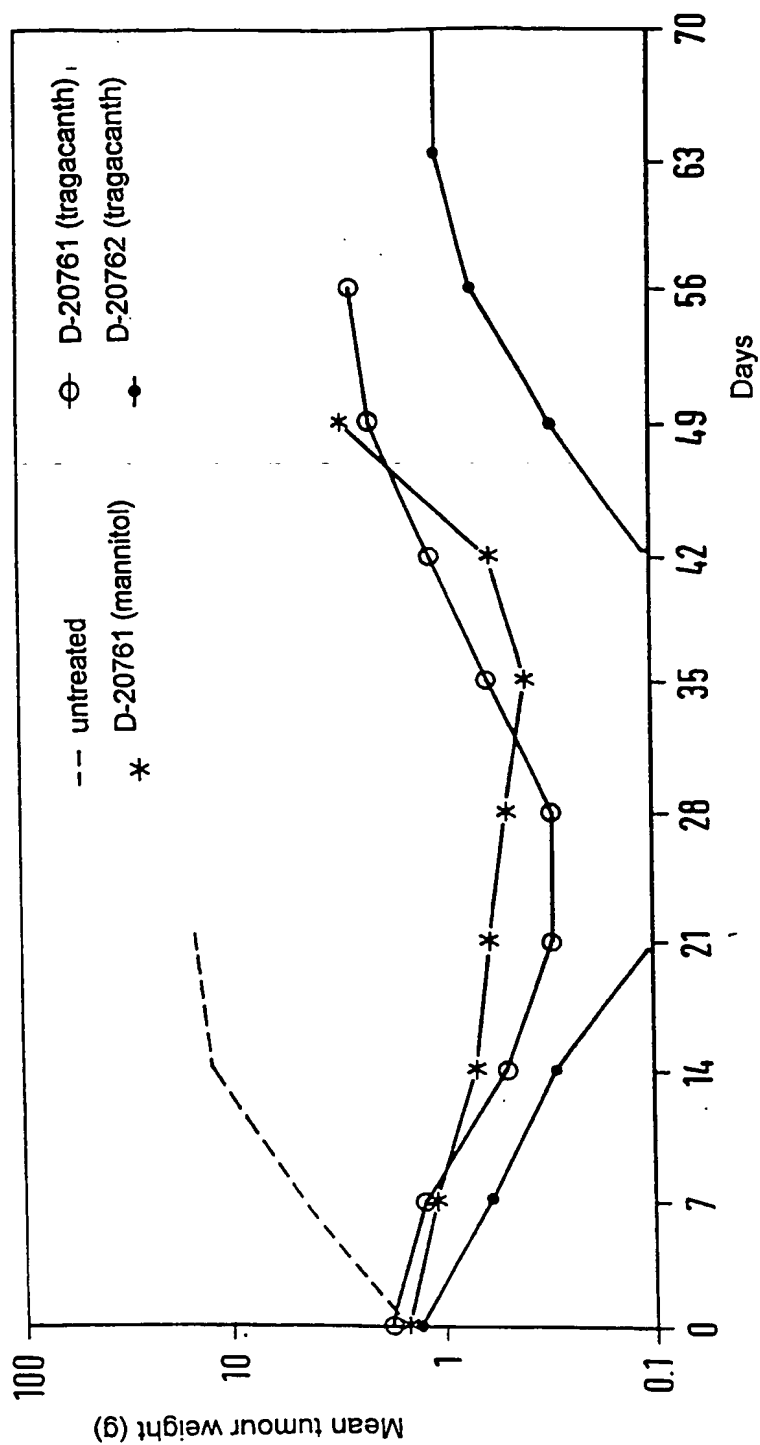
12. Antide embonate, characterized in that it has a particle diameter between 10 um and 125 um.
- 5 13. Ganirelix embonate, characterized in that it has a particle diameter between 10 um and 125 um.
- 14 A-75998 embonate, characterized in that it has a particle diameter between 10 um and 125 um.
- 10 15. Cetrorelix embonate, characterized in that it has a particle diameter between 5 um and 200 um.
- 15 16 Cetrorelix embonate, characterized in that it has a particle diameter between 10 um and 125 um.
17. Cetrorelix embonate, characterized in that it has a particle diameter between 20 um and 125 um.
- 20 18. The use of the salts according to one of Claims 6 to 17 for the preparation of medicaments.
19. A poorly soluble salt of a peptide, characterized in that the particle diameter lies between 5 um and 200 um.
- 25 20. A salt according to Claim 19, characterized in that embonic acid is used as salt former.
21. The use of the salt according to Claim 20 to prepare medicaments.
- 30 22. A poorly soluble salt of a somatostatin analogue, characterised in that the particle diameter lies between 5 um and 200 um.
23. A salt according to Claim 22, characterized in that embonic acid is used as salt former.
- 35 24. The use of the salt according to Claim 23 to prepare medicaments.

25. A poorly soluble salt of a GHRH analogue, characterized in that the particle diameter lies between 5 μm and 200 μm .
- 5 26. A salt according to Claim 25, characterized in that embonic acid is used as salt former.
27. The use of the salt according to Claim 26 to prepare medicaments.
- 10 28. A poorly soluble salt of a bombesin analogue, characterized in that the particle diameter lies between 5 μm and 200 μm .
29. A salt according to Claim 28, characterized in that embonic acid is used as salt former.
- 15 30. The use of the salt according to Claim 29 for the preparation of medicaments.

1/4

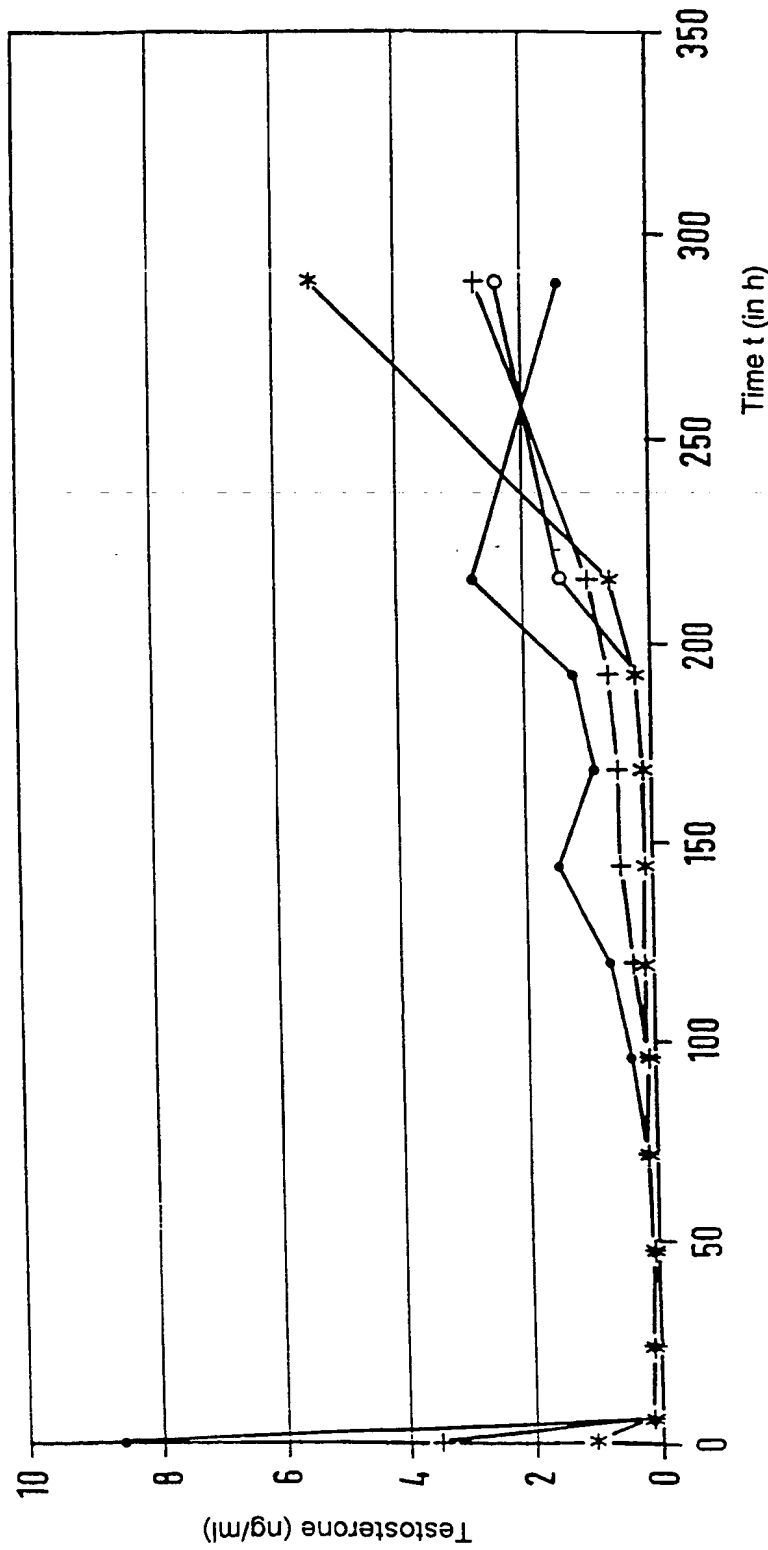
DMBA-induced mama carcinoma

Treatment with a single dose (10 mg/kg) s.c.

**Fig. 1**

2/4

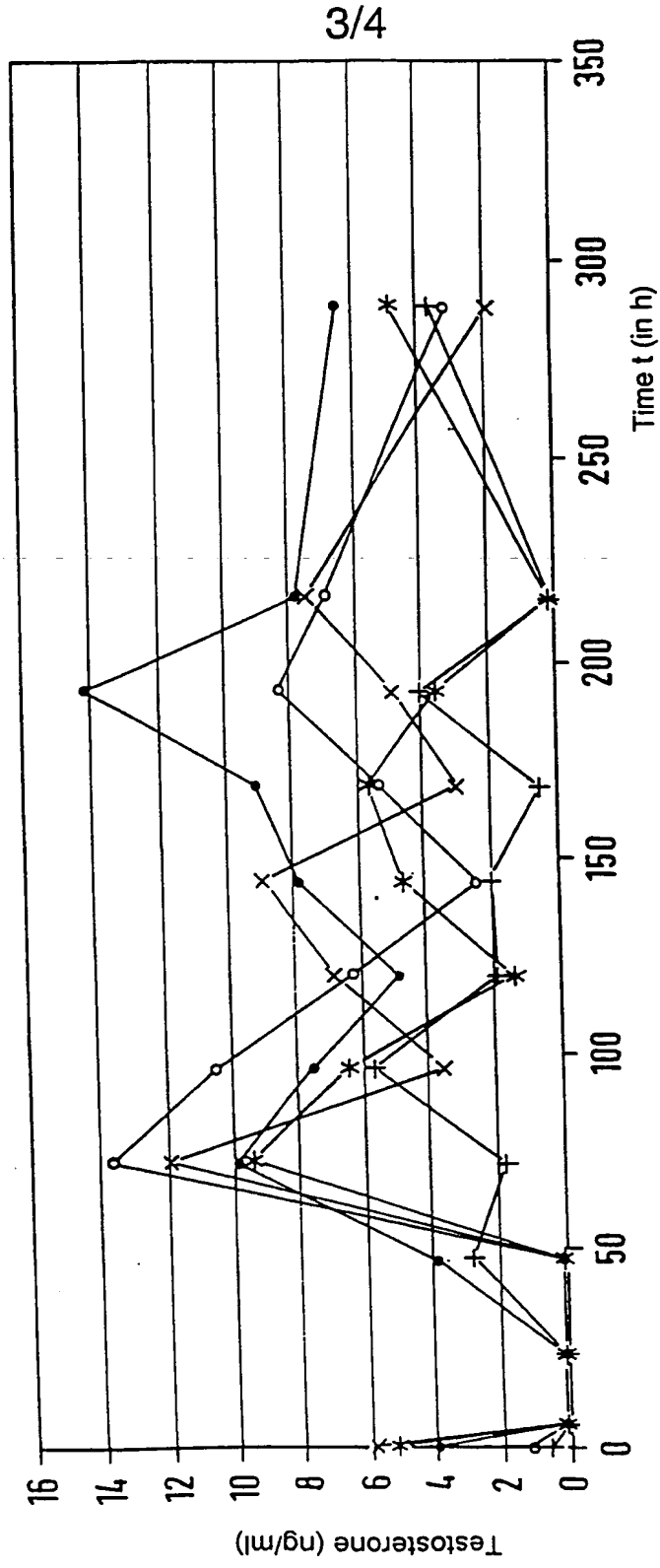
Cetrorelix 0.5 mg/kg s.c. rat
D-20762 (in situ) precipitate without viscous additives



Project 5009
Animal No. 11 Animal No. 12 Animal No. 13 Animal No. 14

Fig. 2

Cetrorelix 0.5 mg/kg s.c. rat.
D-20761 solution in mannitol



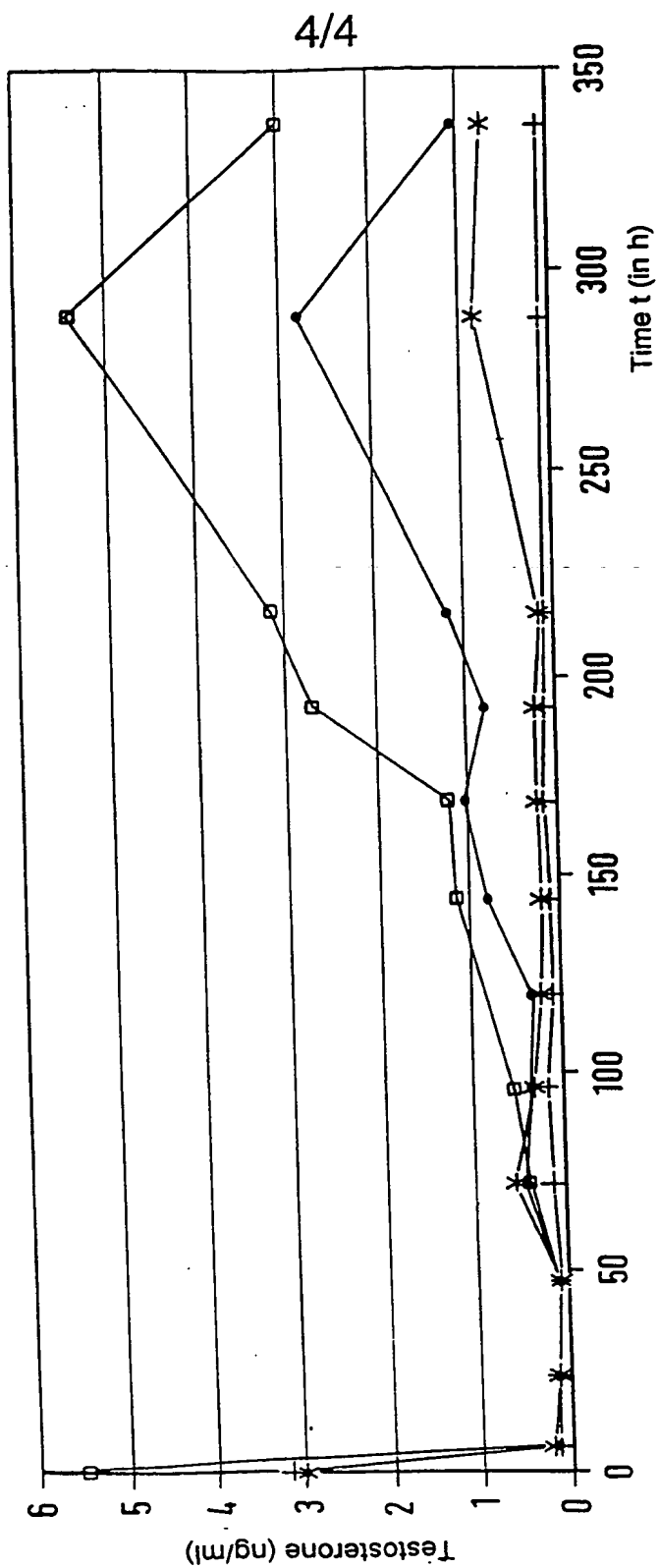
Project 5890

Animal No. 16 Animal No. 17 Animal No. 18 Animal No. 19 Animal No. 20

Animal No. 17, 18: 216 h serum hemolytic

Fig. 3

Cetrorelix 0.5 mg/kg s.c. rat
D-20762 Microparticles RCSES 91-08



Project 5893

Animal No. 31 Animal No. 32 Animal No. 33 Animal No. 34

Fig. 4

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP 94/03904

A. CLASSIFICATION OF SUBJECT MATTER

A 61 K 38/09, A 61 K 38/02, A 61 K 38/10, A 61 K 38/25,
A 61 K 38/31, C 07 K 7/23, C 07 K 2/00, C 07 K 7/08,
C 07 K 14/60, C 07 K 14/655

According to International Patent Classification (IPC) or to both national classification and IPC 6

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

A 61 K, C 07 K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DE, A, 3 822 459 -- (B.P.D. BIOPHARM DEVELOPMENTS LTD.) 30 March 1989 (30.03.89), claims 1-4, 7. --	1-5, 19-27
X	US, A, 5 134 122 (ORSOLINI) 28 July 1992 (28.07.92), claims 1, 2, 8, 10-12, 18. ----	1-5, 19-27



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

13 März 1995

Date of mailing of the international search report

04. 04. 95

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tlx. 31 651 epo nl,
Fax (+31-70) 340-3016

Authorized officer

BÖHM e.h.

ANHANG

zum internationalen Recherchen-
bericht über die internationale
Patentanmeldung Nr.

ANNEX

to the International Search
Report to the International Patent
Application No.

ANNEXE

au rapport de recherche inter-
national relatif à la demande de brevet
international n°

PCT/EP 94/03904 SAE 101148

In diesem Anhang sind die Mitglieder
der Patentfamilien der im obenge-
nannten internationalen Recherchenbericht
angeführten Patentdokumente angegeben.
Diese Angaben dienen nur zur Unter-
richtung und erfolgen ohne Gewähr.

This Annex lists the patent family
members relating to the patent documents
cited in the above-mentioned inter-
national search report. The Office is
in no way liable for these particulars
which are given merely for the purpose
of information.

La présente annexe indique les
membres de la famille de brevets
relatifs aux documents de brevets cités
dans le rapport de recherche inter-
national visé ci-dessus. Les renseigne-
ments fournis sont donnés à titre indica-
tif et n'engagent pas la responsabilité
de l'Office.

Im Recherchenbericht angeführtes Patentdokument Patent document cited in search report Document de brevet cité dans le rapport de recherche	Datum der Veröffentlichung Publication date Date de publication	Mitglied(er) der Patentfamilie Patent family member(s) Membre(s) de la famille de brevets	Datum der Veröffentlichung Publication date Date de publication
DE A1 3822459	30-03-89	AT A 2234/88 AT B 397035 AU A1 22326/88 AU B2 611944 BE AF 1001685 CA A1 1326438 CH A 675968 DE C2 3822459 DK A0 5189/88 DK A 5189/88 ES AF 2009346 FI A0 884297 FI A 884297 FR A1 2620621 FR B1 2620621 GB A0 8722134 GB A1 2209937 GB B2 2209937 GR A 88100619 IE B 60608 IL A0 87790 IL A1 87790 IT A0 8805213 IT A 1225148 JP A2 1121222 LU A 87340 NL A 8802323 NO A0 884154 NO A 884154 PT A 88557 PT B 88557 SE A0 8803321 SE A 8803321 US A 5192741 ZA A 8806827	15-06-93 25-01-94 23-03-89 27-06-91 06-02-90 25-01-94 30-11-90 07-07-94 16-09-88 22-03-89 16-09-89 19-09-88 22-03-89 24-03-89 19-02-93 28-10-87 01-06-89 03-07-91 22-06-89 27-07-94 31-03-89 25-05-92 20-09-88 02-11-90 12-05-89 06-04-89 17-04-89 19-09-88 22-03-89 01-10-88 30-11-92 20-09-88 22-03-89 09-03-93 30-05-89
US A 5134122	28-07-92	AT A 1545/90 AT B 397197 AU A1 59103/90 AU B2 619996 BE AD 1003093 CA AA 2021767 CH A 679207 DE A1 4023134 DK A0 1807/90 DK A 1807/90 ES AF 2020890 FI A0 903643 FR A1 2650182 FR B1 2650182 GB A0 9015722 GB A1 2234169 GB B2 2234169 GR A 90100568 GR B 1001215 IL A0 95120 IL A1 95120 IT A0 9021019 JP A2 3066625 JP B4 6062427 LU A 87772 NL A 9001646 NO A0 903264 NO A 903264	15-07-93 25-02-94 31-01-91 06-02-92 19-11-91 29-01-91 15-01-92 31-01-91 27-07-90 29-01-91 01-10-91 19-07-90 01-02-91 15-05-92 05-09-90 30-01-91 10-02-93 10-12-91 21-06-93 10-06-91 07-10-94 23-07-90 22-03-91 17-08-94 11-12-90 18-02-91 23-07-90 29-01-91

PT	A	94842	20-03-91
SE	AO	9002522	27-07-90
SE	A	9002522	29-01-91
US	A	5225205	06-07-93
ZA	A	9005654	29-05-91
